Clinical Applications of rTMS in Parkinson's Disease

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Abstract

Parkinson's disease (PD) has wide-ranging clinical features, and repetitive transcranial magnetic stimulation (rTMS) therapy has been tried for many aspects of PD. Underlying mechanism of rTMS therapy in PD remains unclear, but several possibilities are proposed such as endogenous dopamine release or restoration of neural plasticity or network activity. Motor symptoms are a cardinal feature of PD, for which evidence suggested moderate efficacy of rTMS. High-frequency (HF) rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1 rTMS) or over the DLPFC, and low-frequency (LF) rTMS over the SMA were most favorable. Long-term administration of levodopa, a major agent for medical therapy of PD, can induce a motor complication called levodopa-induced dyskinesia (LID). Several types of rTMS were reported to be effective for the LID. rTMS has also been tried for non-pharmacological treatment of non-motor symptoms of PD including depression. A "weak recommendation" in favor of HF rTMS of the left DLPFC can be given for the treatment of depressive symptoms associated with PD. These are examples of growing application of rTMS therapy to PD for symptoms other than the classical motor symptoms. As such, rTMS has a potential to become an important adjunctive treatment for PD. Well-designed large clinical trials are needed to establish its utility in the clinical settings.

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9.1 Introduction

Parkinson's disease (PD) has wide-ranging signs and symptoms. It is classically characterized by motor symptoms such as bradykinesia, resting tremor, muscle rigidity, and postural instability (Gibb and Lees 1988); on the other hand, more recent reports have emphasized that various non-motor symptoms can also be a major problem (Chaudhuri et al. 2006). Dopamine depletion resulting from neuronal loss in the substantia nigra of the midbrain plays a crucial role in the motor symptoms, for which dopamine replacement therapy is effective. Prolonged treatment by dopaminergic medicine including levodopa, however, can cause motor complications such as wearing off or levodopa-induced dyskinesia (LID). In addition, dopamine replacement therapy is essentially ineffective for most of the non-motor symptoms. Based on such variation in the clinical presentation of PD, various pharmacological and non-pharmacological therapies have been tried, some of which are successful, such as the deep brain stimulation (Miocinovic et al. 2013). Noninvasive brain stimulation including repetitive transcranial magnetic stimulation (rTMS) can also be a non-pharmacological therapeutic option for PD.

In this chapter, we will pick up several aspects of PD where promising effects of rTMS therapy were reported. Mechanisms underlying clinical utility of rTMS in PD is still yet to be elucidated, but several hypotheses were proposed (Sect. 9.2). On the other hand, clinical studies have demonstrated moderate efficacy of cortical stimulation by rTMS on the motor symptoms (Sect. 9.3). rTMS therapy for the motor symptoms could well be an important adjunctive therapy supporting dopaminergic medication. This chapter will provide a brief overview of rTMS trials in terms of target brain sites and other stimulation parameters. Regarding motor complications (Sect. 9.4) and non-motor symptoms (Sect. 9.5), rTMS has a potential as a novel, key therapy, since these symptoms are sometimes resistant to conventional treatments.

rTMS in itself has few severe side effects, as long as exclusion criteria and dosage limitation for rTMS (Rossi et al. 2009) are strictly observed. A detailed review article has been published with regard to safety issues specific for PD (VonLoh et al. 2013). Researchers applying a brand-new stimulation paradigm should be fully aware of current safety guidelines.

9.2 Mechanisms of rTMS for PD Therapy

What can rTMS do to the dopaminergic system in the brain, a key circuit to treat PD? Dopaminergic cells are situated subcortically such as in the substantia nigra of the midbrain, although (r)TMS can only stimulate cortical neurons (for basic neurophysiology of rTMS, *see* Chap. 1). In this regard, a line of evidence from animal studies showed increased dopamine concentration in the rat striatum by cortical stimulation (Ben-Shachar et al. 1997; Keck et al. 2002). Furthermore, Kanno et al. explored stimulation intensity dependency of the dopamine increase (Kanno et al. 2004). A session of rTMS at approximately 110 % of the motor threshold induced

significant dopaminergic enhancement in the dorsal striatum. Interestingly, however, rTMS with lower or higher stimulus intensity did not modulate the dopamine level at all. This nonlinear stimulus intensity dependency should perhaps be taken into account to establish a novel stimulation protocol. In fact, positive results have been reported in clinical trials using stimulus intensity around the motor threshold (Elahi and Chen 2009).

Human as well as monkey studies with the positron emission tomography also suggested dopamine secretion in the striatum by rTMS (Strafella et al. 2003; Ohnishi et al. 2004), but patient studies so far are not very promising. In early PD patients with unilateral symptoms, rTMS over the primary motor cortex (M1) contralateral to the symptomatic side did decrease [^{11}C] raclopride-binding potential in the putamen, suggesting increased dopamine level in the putamen (Strafella et al. 2005). The amount of the decrease, however, was significantly less than that induced by rTMS over the other primary motor cortex. Thus, it could be the case that the severer degeneration of the dopaminergic system was, the less dopamine increase rTMS could bring about.

Alteration in the neural plasticity or excitability under abnormal dopaminergic function might be restored by rTMS. When applied over the human M1, rTMS is shown to induce excitability change lasting minutes to hours. It is generally assumed that high-frequency (HF; 5 Hz or higher) rTMS increases (Pascual-Leone et al. 1994b; Peinemann et al. 2004), and low-frequency (LF; 1 Hz or lower) rTMS decreases (Chen et al. 1997; Romero et al. 2002) the excitability of the M1. Later researches showed that the rTMS-induced excitability change had several key features in common with synaptic plasticity such as long-term potentiation (LTP) or depression (LTD). In PD, various types of altered neural plasticity has been reported, some of which were related to behavioral dysfunctions. However, meaning of altered plasticity-like effect as indexed by motor cortical excitability change in the behavioral context remains to be investigated. Importantly, clinical benefit does not always go parallel with changes in physiological markers (Koch 2013).

Cellular and molecular mechanism underlying rTMS therapy has been proposed in several animal studies. A research demonstrated that rTMS therapy to 6-hydroxydopamine (OHDA) induced parkinsonian rat improved the motor symptoms and was associated with lower level of tumor necrosis factor-alpha and cyclooxygenase-2 (Yang et al. 2010). The authors discussed that rTMS can improve the motor symptoms by inhibiting inflammatory process. A later study, also conducted on a rat model of PD by 6-OHDA, reported increased expression of various neurotrophic and growth factors (Lee et al. 2013). Interestingly both studies reported that dopaminergic cell loss can be prevented by multiple sessions of rTMS.

9.3 rTMS Therapy for Motor Symptoms of PD

After the first attempt to apply HF rTMS to PD patients (Pascual-Leone et al. 1994a), quite a few clinical studies have been performed to investigate clinical effects of rTMS on motor symptoms in PD patients. Motor symptoms are the key

features of PD, for which the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn et al. 1987) part III has been accepted as a measure in clinical trials. There are two meta-analyses on rTMS therapy for the motor symptoms of PD, using the UPDRS part III as the outcome measure (Fregni et al. 2005; Elahi and Chen 2009). In the first meta-analysis (Fregni et al. 2005), 224 patients were pooled from 12 citations, whose mean (standard deviation, SD) Hoehn and Yahr stage was 2.4 (0.8). Stimulation protocols, such as target brain sites, stimulation frequency, stimulation intensity, total number of pulses, and number of sessions, were quite variable. The authors revealed an overall favorable effect from the pooled results of 8 controlled studies: the pooled effect size (95 % confidence interval, 95 % CI) was 0.60 (0.24, 0.96) based on the random effect model. Assessment took place immediately after the treatment. They argued against a possible publication bias based on results of the funnel plot. The issue of stimulation frequency was further investigated in the second meta-analysis, where studies using HF and LF rTMS were analyzed separately (Elahi and Chen 2009). In total 275 patients were included from 10 studies, whose baseline Hoehn and Yahr stages were between 1 and 4. The result showed efficacy of HF rTMS: the pooled mean effect size (95 % CI) was 0.58 (0.27, 0.90), in favor of rTMS, whereas effects of LF rTMS were too variable to draw any firm conclusion. Influence of other stimulation parameters including target brain site or stimulation intensity still remains to be elucidated. Some results are summarized in the Table 9.1 for blinded randomized controlled studies published after these two meta-analyses.

In this section, we try to characterize the results of clinical trials according to target brain regions. A target site would be the first parameter we have to take into account. Neuroimaging studies have revealed several cortical areas whose activities were different in PD patients from those in healthy people. Although it is generally assumed that cortical activity is decreased under dopaminergic neuron degeneration (Alexander et al. 1986; DeLong and Wichmann 2007), different patterns of brain activation were reported (Playford et al. 1992; Jenkins et al. 1992; Rascol et al. 1992; Sabatini et al. 2000; Yu et al. 2007; Tessa et al. 2010). The M1 and prefrontal cortex have been two common target sites, and studies on other premotor areas were also published.

9.3.1 rTMS over the Primary Motor Cortex (M1)

The M1 has been the most common target site in rTMS therapy for the motor symptoms of PD. It is not severely damaged in PD from the pathological point of view, but plays an important role in motor symptoms in PD via dense connection with other motor-related cortical and subcortical areas. A classical model for the pathophysiology of PD postulated decreased activity in the motor thalamus and resulting hypoactivation in the cerebral cortex including the M1 (Alexander et al. 1986; DeLong and Wichmann 2007). Some neuroimaging studies supported this notion by showing decreased activity in the M1 (Rascol et al. 1992; Buhmann et al. 2003; Tessa et al. 2010), whereas others demonstrated hyperactivity in the M1 (Haslinger

Table 9.1 A summary of blinded randomized controlled trials

Reference	Population[a]	Interventions	Main results
Cardoso et al. (2008)	21 PD patients with depression (1) rTMS group ($N=11$): 67 (8.3) years old, 11 (7.6) years duration, Hoehn and Yahr stage 2.54 (0.82) (2) Fluoxetine group ($N=10$): 63 (7.1) years old, 11 (6.4) years duration, Yahr 2.50 (0.53)	(1) DLPFC rTMS with placebo: 50 trains of 15 s duration at 120 % MT and 5 Hz frequency (3750 pulses) (2) Sham rTMS with fluoxetine (20 mg/day) Three sessions per week for 4 weeks (12 sessions in total)	No improvement in the UPDRS BDI and HRSD improved in both groups
Hamada et al. (2008)	88 PD patients (1) SMA group ($N=55$): 65.3 (8.9) years old, 8.1 (4.2) years duration, Hoehn and Yahr stage 2–4 (2) Sham group ($N=43$): 67.4 (8.5) years old, 7.8 (6.7) years duration, Hoehn and Yahr stage 2–4	(1) SMA rTMS: 20 trains of 10 s duration with 50 s intervals at 5 Hz and 110 % AMT for a leg muscle (1000 pulses) (2) Sham rTMS 8 times weekly	Significant improvement in the UPDRS part III at least up to 12 weeks
Filipović et al. (2009)	10 PD patients with dyskinesia, a crossover study with a minimum of 2-week interval. 64.5 (9.5) years old, 15.6 (5.7) years duration	(1) Real rTMS: 3 series of 600 stimuli at just below AMT and 1 Hz frequency with 1 min intervals (2) Sham rTMS 4 consecutive days	Significant improvement of dyskinesia on the next day of the last stimulation from the baseline only in the real rTMS group
Koch et al. (2009)	20 PD patients with dyskinesia 64.7 (6.9) years old, 10.4 (4.3) years duration	(1) Cerebellar cTBS: 2 trains of 40 s cTBS (600 pulses each) with a 2 min interval at 80 % AMT (2) Sham cTBS 10 sessions (5 sessions per week)	Improvement in the dyskinesia up to 4 weeks
Filipović et al. (2010)	10 PD patients with dyskinesia, a crossover study with a minimum of 2-week interval. 64.5 (9.5) years old, 15.6 (5.7) years duration Hoehn and Yahr stage 3.3 (0.67)	(1) Real rTMS: 3 series of 600 stimuli at just below AMT and 1 Hz frequency with 1 min intervals (1800 pulses) (2) Sham rTMS 4 consecutive days	No improvement in the UPDRS part III assessed in the "off" state

(continued)

Table 9.1 (continued)

Reference	Population[a]	Interventions	Main results
Pal et al. (2010)	22 PD patients with depression (1) Actively treated group ($N=12$): 68.5 years old, 6.0 years duration (2) Sham group ($N=10$): 67.5 years old, 6.5 years duration	(1) Left DLPFC rTMS: 12 trains of 10 s duration with 20 s intervals (600 pulses) at 90 % RMT and 5Hz frequency (2) Sham rTMS 10 sessions	Significant improvement of depression 30 days after treatment Trend-wise improvement in UPDRS part III
Benninger et al. (2011)	26 PD patients. (1) iTBS group ($N=13$): 62.1 (6.9) years old, 10.8 (7.1) years duration, Yahr 2.6 (0.2) (2) Sham group ($N=13$): 65.6 (9.0) years old, 6.5 (3.4) years duration, Yahr 2.5 (0.1)	(1) iTBS over the M1 and DLPFC with a circular coil (2) Sham TBS 8 sessions (2 weeks, a daily session for 4 consecutive days/week)	No effects on the UPDRS-III Improvement in the mood
Benninger et al. (2012)	26 PD patients (1) 50 Hz group ($N=13$): 64.5 (9.1) years old, 8.6 (4.1) years duration, Yahr 2.4 (0.2) (2) Sham group ($N=13$): 63.7 (8.3) years old, 9.3 (6.8) years duration, Yahr 2.5 (0.3)	(1) 50 Hz rTMS: 6 s duration rTMS with a circular coil at 80 % AMT and 50 Hz frequency to both M1s (300 pulses each) (2) Sham rTMS 8 sessions (4 consecutive days/week)	No improvement in motor symptoms
Shirota et al. (2013)	106 PD patients (1) 1 Hz SMA ($N=36$): 68.8 (7.6) years old, 8.5 (7.3) years duration, Yahr 2–4 (2) 10 Hz SMA ($N=34$): 67.9 (8.4) years old, 7.8 (6.6) years duration, Yahr 2–4 (3) Sham rTMS ($N=36$): 65.7 (8.5) years old, 7.6 (4.4) years duration, Yahr 2–4	(1) 1 Hz SMA: a single session at 1 Hz (1000 pulses) (2) 10 Hz SMA: 20 trains of 5 s duration at 10 Hz (1000 pulses) (3) Sham rTMS Stimulus intensity: 110 % AMT for a leg muscle (if this was higher than 110 % RMT for a hand muscle, the latter was chosen) 8 sessions weekly	Improvement in the UPDRS-III lasted up to 20 weeks in 1 Hz group. Improvement in 10 Hz and sham returned to the baseline after treatment

HRSD Hamilton rating scale for depression, *BDI* Beck depression inventory, *AMT* active motor threshold, *MT* motor threshold

[a]Age, disease duration, and Hoehn and Yahr stage are presented as mean (standard deviation), whenever possible

et al. 2001; Eckert et al. 2006; Yu et al. 2007). As mentioned in Sect. 9.2, rTMS over the M1 is supposed to be able to increase or decrease the excitability of the M1, dependent on the stimulation frequency; both types of rTMS have been thus tried.

Animal studies also supported potential efficacy of M1 stimulation. HF electrical stimulation of the M1 was effective in the nonhuman primate model (Drouot et al. 2004). In rodent studies it is often difficult to stimulate a specific brain area by rTMS, but Gradinaru et al. elegantly demonstrated that depolarization of the motor cortex can be a good treatment option for PD (Gradinaru et al. 2009). They reported that selective HF depolarization of the layer V pyramidal neurons in the M1 had similar behavioral effects as artificial electric stimulation of the subthalamic nucleus, which is one of the major targets of the deep brain stimulation. These results suggest that long-lasting electrophysiological change in the M1 can ameliorate the motor symptoms of PD.

It is difficult to draw a firm conclusion from the results of currently available clinical trials mainly because of variable stimulation protocols and small number of participants in each trial. Several studies with HF rTMS reported improvement in the UPDRS motor score (Siebner et al. 2000; Khedr et al. 2003; Lefaucheur et al. 2004), whereas some others reported no clinical benefit (Rothkegel et al. 2009; Benninger et al. 2012). Variation in stimulus parameters among studies (e.g., some used 5 Hz, others used 10 Hz) defies any generalization, and total number of patients studied is very small. On the other hand, most of LF rTMS over the M1 failed to show positive effects (Okabe et al. 2003; Rothkegel et al. 2009; Filipović et al. 2010), with some exception (Lefaucheur et al. 2004). Compared with stimulus frequency, dimension of stimulus intensity is less explored. Regardless of frequency, higher intensity such as 120 % of resting motor threshold tended to be effective (Sommer et al. 2002; Khedr et al. 2003), but positive results were also reported in two studies using stimulus intensity as low as 80 % of it (Lefaucheur et al. 2004; González-García et al. 2011). Mally et al. investigated impact of stimulus intensity using 1 Hz rTMS and found a nonlinear relationship: rTMS with 0.57 tesla had significant effect, whereas that with higher (0.80 tesla) or lower (0.34 tesla) intensity did not improve the motor function (Mally and Stone 1999). When targeting the "M1" focally with TMS, there can be several possibilities: right and left M1 for a hand representation and leg M1. Whereas most studies stimulated uni- or bilateral hand M1, Khedr et al. combined all of the three and reported good efficacy (Khedr et al. 2003, 2006, 2007). Lastly, temporal distributions of rTMS sessions can also be pointed out as an important factor. Some studies used single, whereas others multiple, rTMS sessions. Among studies on multiple rTMS sessions, most applied daily rTMS sessions 4–10 times for 1 or 2 weeks, with some exception, e.g., weekly rTMS 8 times (Okabe et al. 2003). Accordingly the follow-up period is variable, too. In general multiple rTMS sessions are favorable, but this is not always the case. In this regard, two LF rTMS studies are contradictory. Lefaucheur et al. reported effect of a single rTMS session (Lefaucheur et al. 2004); on the contrary Okabe et al. reported no improvement with weekly rTMS sessions compared with sham rTMS (Okabe et al. 2003).

In addition to "conventional" rTMS described above (e.g., 1 Hz rTMS or 5 Hz rTMS), so-called "patterned" rTMS has been introduced more recently. Among several patterned rTMS protocols, theta-burst stimulation (TBS) is most widely studied (Huang et al. 2005). A TBS session requires less time than conventional rTMS, nevertheless seems as effective (Zafar et al. 2008). Most of clinical studies, however, were not as promising (Rothkegel et al. 2009; Benninger et al. 2011; Degardin et al. 2012). A single session of intermittent TBS (iTBS, supposed to induce LTP-like plasticity) improved bradykinesia and rigidity mildly (Degardin et al. 2012), but no efficacy was shown in the UPDRS in a randomized, double-blind, sham-controlled study (Benninger et al. 2011). The negative findings can be partly attributed to altered response to rTMS in PD. Studies investigating plasticity induction in PD patients in general reported ineffectiveness or responses different from healthy populations (Eggers et al. 2010; Suppa et al. 2011; Kishore et al. 2012a). A recent study even demonstrated that responses to TBS are highly variable in the healthy population (Hamada et al. 2013).

Indeed, at least two other factors should be taken into account for explaining the variable effects of rTMS in PD: medication and aging. First, aftereffect of brain stimulation is influenced by simultaneous administration of central nervous system-acting drugs. Especially, levodopa, which is very often administered to PD patients requiring additional therapy such as rTMS, has been found to affect several noninvasive brain stimulation protocols in a dose-dependent manner (Monte-Silva et al. 2010; Thirugnanasambandam et al. 2011). Second, effects of rTMS have been mainly demonstrated and investigated in healthy young participants; some more recent researches, however, elucidated age-related decline in the effect of rTMS (Müller-Dahlhaus et al. 2008; Fathi et al. 2010; Bashir et al. 2014). It can be the case that older patients taking medications such as levodopa do not respond to an rTMS protocol as expected in a younger healthy population.

9.3.2 rTMS over the Prefrontal Cortex

The second often investigated brain site is the dorsolateral prefrontal cortex (DLPFC). Clinical trials using DLPFC rTMS most commonly targeted PD patients with depression (Sect. 9.5), but influence on the motor function is reported as well. HF rTMS was most often applied over the left DLPFC. An open study demonstrated significant improvement in the UPDRS part III score (Epstein et al. 2007). Pal et al. reported a large amount of improvement in the UPDRS motor score (7.5 points) in a randomized double-blind study, but it did not reach a statistically significant level (Pal et al. 2010). Other studies did not find significant effect of DLPFC rTMS on the motor symptoms (Fregni et al. 2004; Boggio et al. 2005). It is still more controversial whether rTMS over the DLPFC can improve motor symptoms of PD without depression (Dias et al. 2006; del Olmo et al. 2007). There may be difficulty to discriminate mood-related motor improvement and "true" improvement of motor function; rTMS over the DLPFC, however, would be very efficient if it can ameliorate both motor and non-motor functions. More recently, an open-label study reported

effectiveness of prefrontal rTMS (Spagnolo et al. 2014). The authors targeted both the M1 and bilateral prefrontal regions with "deep" rTMS at 10 Hz frequency using a specialized stimulation coil termed H-coil. Twelve sessions over 4 weeks yielded positive effect. Further controlled studies are needed for this new technique.

9.3.3 rTMS over Other Frontal Areas

Between the M1 and the DLPFC lie so-called secondary motor areas such as the supplementary motor area (SMA) and the dorsal premotor cortex (PMd), which have not attracted much interest as target sites for rTMS therapy in PD. A common assumption here is deactivation of the SMA (Playford et al. 1992; Jenkins et al. 1992; Rascol et al. 1992; Buhmann et al. 2003) and hyperactivity in the PMd (Samuel et al. 1997; Sabatini et al. 2000). Therefore, a study by Boylan et al. was surprising in that an HF (10 Hz) rTMS over the SMA, which was supposed to increase SMA activity, worsened motor function (Boylan et al. 2001). A clue might exist in a study on a healthy population where worsening of a motor behavior was induced by HF rTMS over the SMA (Gerloff et al. 1997). Behavioral effects of rTMS might be different from physiological effects. Furthermore, the role of SMA in PD is somewhat complex. The hypoactivation has been reported during a cued simple motor task; on the other hand, hyperactivity of the anterior SMA during a complex motor task (Catalan et al. 1999) or self-initiated movement (Eckert et al. 2006) has been reported. One study revealed deep brain stimulation-induced reduction of SMA activity paralleled with learning efficiency, discussing a potential role of overactive SMA-subthalamic nucleus network in PD (Mure et al. 2012). These complicated results might be a reason why not so many researchers were lured by SMA rTMS as a therapy for PD.

Two multicenter clinical trials from Japan have revealed significant improvement of the motor symptoms in PD compared with sham stimulation. In the first trial, 5 Hz rTMS over the SMA was delivered in 99 PD patients (Hamada et al. 2008, 2009). An rTMS session with 1000 pulses was repeated 8 times weekly. Stimulus intensity was set at 110 % AMT for a leg muscle. The real rTMS group showed approximately 4-point improvement in the UPDRS part III, in contrast with almost no change in the sham group. The later study explored stimulus frequency dependency of the SMA rTMS using similar parameters (Shirota et al. 2013). In total 106 patients were randomly assigned to 10 Hz rTMS, 1 Hz rTMS, or the sham stimulation groups. Contrary to evidence from M1 rTMS, it was the 1 Hz (i.e., LF) rTMS that improved the motor symptoms best; improvement in the 10 Hz rTMS group was not significantly different from that in the sham group. The beneficial effect of the 1 Hz rTMS lasted at least 12 weeks after the end of the treatment. In future studies, it would be more fruitful to try rTMS with 5 Hz or slower stimulus frequency when targeting the SMA. Both effects of 5 and 1 Hz rTMS should be replicated in another independent clinical trial to establish their efficacy.

Regarding the PMd, we can find only several open-label studies with a small sample size. Buhman et al. applied 1200 pulses of 1 Hz rTMS over the PMd at 80 %

AMT and reported significant improvement in the UPDRS of mild to moderate PD patients (Buhmann et al. 2004). On the other hand, the same rTMS paradigm did not improve motor functions of more advanced patients (Bäumer et al. 2009). High-frequency, 5 Hz rTMS was reported to be ineffective for clinical symptoms (Mir et al. 2005).

9.3.4 Short Conclusions

Taken together, it is likely that rTMS is moderately effective for motor symptoms of PD, but that several issues need to be clarified. Stimulation parameters, such as a target region, stimulation frequency, and stimulation intensity, and stimulation schedule (e.g., daily, weekly) should be refined further. So far the evidence suggests that HF rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1) or DLPFC with 6–12 sessions, and LF (1 Hz) rTMS of the SMA with a weekly schedule for 8 weeks were most favorable for the treatment of motor symptoms in PD. There are responders and nonresponders for a certain rTMS protocol even in healthy, relatively young people (Hamada et al. 2013). Considering the great variability in the clinical presentation of PD including age, disease duration, prominent symptom, and medication, some strategy to find out responders may be needed, or stimulation protocol should be adjusted to each patient. Further, larger controlled studies are also needed to establish the therapeutic effect of rTMS on the motor symptoms.

Given the variability of methods used and of the results across trials, "no (firm) recommendation" (Guyatt et al. 2008) can be given in favor of rTMS therapy for motor symptoms of PD.

9.4 Levodopa-Induced Dyskinesia (LID)

Long-term levodopa therapy often poses a problem called motor complications including LID. In a prospective study, its incidence was reported as high as 45 % of PD patients treated with levodopa for years (Rascol et al. 2000). If a patient develops LID, physicians may be more or less reluctant to increase dopaminergic medication (Fabbrini et al. 2007; Rascol et al. 2000), resulting in suboptimal treatment. Therefore, importance of seeking treatments for the LID may be twofold: decrease of LID can in itself improve the quality of life (QOL) and allow the dopaminergic treatment at a more desirable level.

A line of evidence has shown a pivotal role of abnormal synaptic plasticity in the LID; the plasticity-like effect induced by rTMS may therefore be a good treatment option. Dopamine depletion first abolishes plastic changes at the corticostriatal synapses. The LTP, however, can be restored following chronic dopamine substitution. Intriguingly, this synaptic potentiation could be reversed in PD rats without the LID by low-frequency stimuli which usually cause LTD in a "neutral" synapse, whereas presence of LID was closely associated with loss of this "de-potentiation," showing

overactivity of the synapses (Picconi et al. 2003). Evidence from the human M1 has also elucidated several types of altered plasticity-like effect in PD patients with LID (Huang et al. 2011; Kishore et al. 2012b; Morgante et al. 2006). Clinically, the overactivity of the corticostriatal synapses might be related to excess of abnormal involuntary movements in the LID, and reducing it might be a potential target for treatment of the LID.

Several clinical trials of rTMS therapy for the LID targeted frontal brain areas based on human neuroimaging studies demonstrating altered, mainly hyperactive, brain function in PD with LID (Rascol et al. 1998). Koch et al. for the first time demonstrated influence of single-session SMA rTMS on the LID. In compatible with the notion of cortical hyperactivity, 1 Hz rTMS, supposed to decrease the activity of the SMA, reduced the LID, whereas 5 Hz, presumably "excitatory," rTMS induced trend-wise worsening (Koch et al. 2005). A following research from the same group, however, revealed that the effect did not have a cumulative effect with 5 daily sessions (Brusa et al. 2006). A more recent 10-day rTMS trial also reported short-lasting beneficial effect of low-frequency rTMS over the SMA (Sayin et al. 2014). Another strategy would be to decrease activity in the M1, but researches have shown only transient or mild effect of M1 rTMS (Wagle-Shukla et al. 2007; Filipović et al. 2009).

Cerebellar TBS was introduced by Koch et al. as a treatment option for the LID, which seems to have the best efficacy so far (Koch et al. 2009). A 10-day course of the cTBS sessions (5 days a week for 2 weeks) improved the LID compared with a sham cTBS course for at least 4 weeks. Further investigations are warranted on this protocol.

While some of the reports mentioned are encouraging, so far "no recommendation" (Guyatt et al. 2008) can be given in favor of rTMS therapy for LID in PD in routine clinical practice.

9.5 Non-motor Functions

More and more attentions have been paid to non-motor symptoms of PD. Some researchers reported that the non-motor symptoms affect the QOL more than the motor symptoms and that they are very often overlooked (Chaudhuri et al. 2010; Zesiewicz et al. 2010). Most of them do not respond to dopaminergic therapies. The non-motor symptoms of PD include neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal symptoms, and sensory symptoms (Chaudhuri et al. 2006).

Among the non-motor symptoms of PD, depression is currently the best responding symptom to rTMS. The strategy is closely related to rTMS therapy for major depression in the field of psychiatry. High-frequency rTMS over the left DLPFC and low-frequency rTMS over the right DLPFC are two major options (Padberg and George 2009), and high-frequency rTMS has been mainly tried in PD patients. In a relatively large sham-controlled study on 42 PD patients with depression, influence of 10 sessions HF (15 Hz) rTMS of the left DLPFC on depression was comparable with that of the selective serotonin reuptake inhibitor

fluoxetine, while rTMS was associated with less side effects and greater motor and cognitive improvement (Fregni et al. 2004). High-frequency rTMS can improve the mood in PD without any apparent side effects in other cognitive domains (Boggio et al. 2005). A more recent study reported differential influence of rTMS and an antidepressant on regional brain activity using fMRI, which suggests potential add-on effects of rTMS combined with antidepressants (Cardoso et al. 2008). A subsequent double-blind sham-controlled study further confirmed significant improvement of depression as well as trend-wise effect on motor function (Pal et al. 2010). Ten sessions of 5 Hz rTMS over the left DLPFC led to a considerable improvement on depression rate scales as well as motor scores 30 days after treatment ended.

The data from the two larger controlled clinical trials warrant a "weak recommendation" (Guyatt et al. 2008) in favor of HF rTMS of the left DLPFC in the treatment of depressive symptoms associated with PD.

9.6 Summary and Future Directions

Treatment of PD requires a multidisciplinary approach in which rTMS can be involved. We need, however, further research, especially large-scale clinical studies, to establish clinically meaningful utility of rTMS therapy.

For motor symptoms, we can find several well-designed clinical trials, but their overall efficacy is only moderate. HF rTMS over the M1 including less focal stimulation (e.g., leg and bilateral hand M1 rTMS) or over the DLPFC, and LF rTMS over the SMA were most favorable so far. Since motor symptoms of PD can be successfully treated by dopaminergic medications in many cases, more benefit is needed for the rTMS therapy to be a major therapeutic option.

Positive results that need further elaboration and confirmation were also reported in relatively small studies for some of the motor complications such as LID.

An evidence-based "weak recommendation" (Guyatt et al. 2008) in favor of HF rTMS of the left DLPFC can be given for the treatment of depressive symptoms associated with PD.

In each of the domains, further evidence is required in larger studies. Several factors, including, but not limited to, aging of the brain, variation in clinical presentation, or influence of medication, should be taken into account in investigating newer stimulation paradigm. Basic understanding of mechanisms of rTMS would be another prerequisite for future successful clinical trials.

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